IPEA
European Patent Office
Directorate General 2
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GERMANY

23 October 2001

Sent by fax

Dear Sirs

PCT Patent Application No. PCT/GB00/03196
IMPERIAL COLLEGE INNOVATIONS LIMITED
Our ref: ICOY/P23294PC

This is a response to the Written Opinion dated 25 September 2001.

The following numbered sections correspond to the equivalent sections of the Written Opinion.

III 2 We do not wish to respond to this objection at this stage.

IV We disagree with the examiner's finding that there are four inventions. We submit that at least the first three inventions identified by the examiner are linked by the concept of the use of a SNARE polypeptide in medicine. Although naturally occurring SNAREs and toxin-resistant SNAREs are known, there is no teaching or suggestion in the documents cited by the examiner of medical uses of these polypeptides. Accordingly, we submit that the examiner's objection of lack of unity is incorrect at least in relation to inventions 1 to 3 as identified by the examiner in the written opinion and in the Invitation to pay additional fees dated 23 February 2001.

V 3.1 We disagree with the examiner's finding that a method of reversing the inhibition of exocytosis in a cell caused by contact of a clostridial toxin

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with the said cell is taught by Gonelle-Gispert *et al* (1999) *Biochemistry J* **339**, 159-165 (D1) or Sadoul *et al* (1997) *J Biol Chem* **272**, 33023-33027 (D2).

The examiner will note that claim 3 (and therefore claims when dependent on claim 3) requires that the SNARE is supplied to the cell not before contact of the clostridial toxin with the cell. In both D1 and D2, the SNAREs are supplied to the cell before contact of the clostridial toxin with the cell. For example, on page 162 of D1, second column, second paragraph, it is stated that "[a]fter transfection (2 days) the cells were permeabilized and treated with 30 nM BoNT/E to inactivate the endogenous SNAP-25." (emphasis added). Similarly, D2 states in the legend to Figure 2 that "HIT cells were transiently co-transfected with human proinsulin and SNAP-23 or SNAP-25. Two days after transfection, cells were permeabilised with SLO and incubated with or without 30 nM BoNT/E" (emphasis added). Thus, it is clear that in both D1 and D2 the supply of SNARE to the cell occurs before contact of the clostridial toxin with the cell. There is no reversal of inhibition. Thus, neither D1 nor D2 deprives claim 3 or dependent claims of novelty.

The examiner appears to consider that claim 30 encompasses a replacement mutant of full-length SNAP-25. We submit that the examiner has misinterpreted the scope of claim 30, which we submit clearly would be understood to require that the polypeptide consists of residues identical to residues 1 to 198, 199, 200 or 201 of (either) full length SNAP-25 or a variant thereof, or a fusion either thereof. Thus, we submit that D1 does not deprive claim 30 of novelty.

V 3.2 We note that the examiner's comments on claims 2, 13-15, 25 and 32 are not relevant when these claims are considered in accordance with EPO practice, for example as noted by the examiner in section III 3 of the written opinion. Claim 2 (from which claims 13 to 15 depend) is in the "second medical use" format. Claim 25 and 32 are in the "first medical use" format. These formats are discussed in the "Guidelines for Examination in the European Patent Office", for example in Part C, Ch IV, Section 4.2 of the February 2001 edition. Neither D1 nor D2 teach nor suggest the use of SNAREs for treating botulism or any other medical use; thus, neither D1 nor D2 can deprive these claims of novelty at least under EPO practice.

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As noted in relation to Section V 3.1, D1 does not deprive claim 30 of novelty. Similarly, D1 does not deprive claim 34 (relating in part to a nucleic acid suitable for expressing a polypeptide according to claim 30) of novelty.

Neither D1 nor D2 teach nor suggest the use of recombinant polynucleotides encoding any SNARE for any medical use; thus, neither D1 nor D2 can deprive these claims of novelty at least under EPO practice. Neither D1 nor D2 teach any gene therapy construct comprising a recombinant polynucleotide encoding any SNARE; accordingly, claim 39 is novel over D1 and over D2.

V 4.1 The examiner appears to consider that Brunsd *et al* (1997) *J Neurosci* **17**, 1898-1910 (D3) describes restoration of SNARE based vesicle fusion. We submit that this is not the case. D3 concludes that synaptic transmission is rendered toxin-insensitive as a result of the presence of cleavage resistant forms of SNAP-25. There is no indication of restoration of inhibited function. There is no suggestion or investigation of the effect of supplying the cleavage resistant SNAP-25 to cells in which it does not naturally occur, for example there is no suggestion of supplying it to naturally toxin-sensitive cells.

We submit that claim 1 and dependent claims are inventive. None of D1, D2 or D3 demonstrate any restoration of function in cells which have already been poisoned by clostridial toxin. The examiner will appreciate that restoration of function to a poisoned cell is very different to prevention of loss of function. In the latter case, the SNARE molecule is supplied in a healthy cell with a functional vesicle transport system. In the former case, the SNARE molecule is supplied in a damaged cell with a damaged vesicle transport system.

In contrast, the present application clearly demonstrates rescue of exocytotic function in cells which have already been poisoned by clostridial toxin.

Further, the systems of D1 and D2 are highly non-physiological (for example involving permeabilisation with streptolysin-O). The skilled

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person would not contemplate suggesting any treatment of a patient on the basis of these documents.

V 4.2 In view of the inventiveness of the claims from which they depend, we submit that dependent claims 8, 9, 10 and 11 are in any case inventive.

We submit that claims 29, 31 and 33 are also inventive. The examiner has not indicated any motivation for preparing the particular polypeptides claimed in claim 29 or claim 31, which have been found to be useful as described in the present application. For example, a SNARE in which the residue immediately N-terminal to a clostridial toxin cleavage site is replaced by a cysteine residue is useful because it may form a potent inhibitor of the toxin on cleavage of the SNARE. D2, for example, provides no teaching regarding mutating SNAP-25 in order to minimise susceptibility to toxin cleavage or provide a toxin inhibitor whilst retaining the ability to mediate neuro-exocytosis. Accordingly, claims 29, 31 and 33 are inventive.

V 4.3 In view of the inventiveness of the claims from which it depends, claim 16 is in any case inventive. Similarly, claim 45 is also inventive. None of the cited documents provide any motivation for providing a kit of parts as claimed in claim 45.

V 4.4 In view of the novelty and inventiveness of claims 29 to 31, we submit that the method of claim 35 is also inventive.

V 4.5 The examiner has indicated no motivation for providing a molecule as defined in claim 26. We submit that before the work described in the present application, there was no motivation to provide such a molecule.

As noted above, claim 39 is novel and inventive.

Accordingly, we submit that dependent claims 27, 28 and 42 are also novel and inventive.

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VII We enclose replacement claim 10 which we submit addresses the examiner's concerns.

VIII 1 and 2 We enclose replacement claims 2, 11, 29, 31 and 45 which we submit address the examiner's concerns.

VIII 3 We do not wish to address this objection at this stage.

Any amendment is not to be construed as abandonment of subject matter.

We look forward to receipt of a favourable International Preliminary Examination Report.

Yours faithfully
ERIC POTTER CLARKSON

JSM

John S Miles PhD sjp/ncr

Enc: Replacement pages 101, 102, 105, 107 and 108